EXHIBIT 15

Gynecologic Oncology: *Original Research*

Risk of Gynecologic Cancer According to the Type of Endometriosis

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OBJECTIVE: To assess the risks of gynecologic cancer according to the type of endometriosis in women with surgically verified endometriosis.

METHODS: This is a population-based study of women with surgically verified endometriosis retrieved from the Finnish Hospital Discharge Register 1987–2012 (N=49,933); the subtypes of ovarian (n=23,210), peritoneal (n=20,187), and deep infiltrating (n=2,372) endometriosis were analyzed separately. Gynecologic cancers were obtained from the Finnish Cancer Registry. The outcome measure was the standardized incidence ratio (95% CI) calculated as the ratio between the observed to the expected number of cancers and defined for each gynecologic cancer and further stratified according to the histology, follow-up time since surgery, and age at follow-up. The follow-up was 838,685 person-years, and the Finnish female population served as the reference.

RESULTS: Endometriosis was associated with increased risk of ovarian cancer (standardized incidence ratio 1.76 [95% CI 1.47–2.08]), especially with endometrioid (3.12 [2.15–4.38]) and clear cell (5.17 [3.20–7.89]) histologic type and to a lesser extent with serous type (1.37 [1.02–1.80]). The risk of ovarian cancer was highest among women with ovarian endometriosis and especially for endometrioid (4.72 [2.75–7.56]) and clear cell (10.1 [5.50–16.9]) ovarian cancer, occurring 5–10 years after the index surgery. The overall risk of ovarian cancer was not increased among women with peritoneal and deep infiltrating endometriosis. However, peritoneal endometriosis was associated with a twofold increase in risk of endometrioid histology. The risk of endometrial cancer was not altered in the entire cohort. The standardized incidence ratio for precancerous cervical lesions was 0.81 (0.71–0.92) and for invasive squamous cell carcinoma of the cervical cancer 0.46 (0.20–0.91).

CONCLUSION: The excess risk of ovarian cancer among women with ovarian endometriosis translates into two excess cases per 1,000 patients followed for 10 years. Acknowledging these risks is important when planning long-term management of women with endometriosis.

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The association between endometriosis and cancer has been studied intensively. Endometriosis is characterized by chronic inflammation, tissue-specific excess production of estrogen, and resistance to progesterone,[1] which characteristics may also predispose to cancer. In addition, endometriosis presents cancer-like characteristics such as tissue invasion, angiogenesis, and decreased apoptosis.[2,3]

An increased risk of ovarian cancer among women with endometriosis has been found in several cohort and case–control studies with relative risk between 1.3 and 1.9.[4–6] The relative risk has been higher for clear cell and endometrioid types of ovarian cancer.[4,7–9] Endometriosis or its atypical form are found in one third of endometrioid and clear cell

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The data were obtained from the Finnish Hospital Discharge Register, the Finnish Cancer Registry, and the Finnish Population Register Center.

Each author has indicated that he or she has met the journal's requirements for authorship.

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ovarian carcinomas.[10,11] Similar molecular changes have been detected in the nearby endometriosis as in the cancer (ie, *ARID1A*, *PTEN*, *HNF1B*, and *PIK3CA K-ras* mutations).[10] Thus, endometriosis is considered to be a risk factor for ovarian cancer or it may act as a precursor lesion for clear cell and endometrioid ovarian carcinomas. Findings suggesting an association of endometriosis and other gynecologic cancers have been less clear.[4,6]

The gold standard for diagnosing endometriosis is surgery.[12] In the present study, we assessed the risk of gynecologic cancers among women with a surgical diagnosis of endometriosis. Because little is known about the risk of cancer related to specific subtypes of endometriosis, the patients were further classified into ovarian, peritoneal, and deep infiltrating endometriosis.

MATERIALS AND METHODS

Before initiation, this population-based study was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa (238/13/03/03/2013). Permission to utilize the data and the linkages was provided by the National Institute for Health and Welfare (THL/546/5.05.00.2014) and the Population Register Center (D1794/410/14), as required by legislation.

The formation and description of the cohort has been described in detail elsewhere.[13] The Finnish Hospital Discharge Register is national and includes personal identity codes, codes of diseases according to the International Classification of Diseases (ICD), and dates for each hospital visit.[14] The data have been collected regularly since 1968 for the cohort population database. The ICD codes are set by the managing clinician for each hospital visit based on their clinical relevance. In the Finnish health care system, ICD codes are primarily for clinical purposes. According to the systematic review, more than 95% of discharges have been identified from the Finnish Hospital Discharge Register.[15] Our quality assessment of the diagnoses of endometriosis in Finnish Hospital Discharge Register records showed 97% to be correctly reported from the hospital to the register and 95% of diagnoses from the register were correctly in our cohort.[13]

To include all surgically diagnosed cases, we collected the present cohort from the Finnish Hospital Discharge Register by using appropriate diagnostic codes for endometriosis (ICD, 9th Revision [1987–1995]: 6171A, 6172A, 6173A, 6173B, 6174A, 6175A, 6176A, 6178X, 6179X; ICD, 10th Revision [1996–2012]: N80.1-N80.6, N80.8, N80.80, N80.81, N80.89, N80.9), as a main or subsidiary diagnosis, in combination with relevant concomitant surgical codes from 1987 to 2012 (N=49,933). The discharge date of the first hospital visit fulfilling the inclusion criteria was used as the index day. The cohort consisted of inpatients from both the public and private sectors. Information on day surgeries was available from 1994 onward. The diagnosis of adenomyosis was not included when existing alone.

The patients were further classified into subcohorts of endometriosis according to the diagnosis determined at the index procedure: ovarian (n=23,210), peritoneal (n=20,187), deep infiltrating (n=2,372), mixed (ovarian and deep infiltrating concomitantly, n=1,120), and other endometriosis (n=3,044) (Table 1). The diagnoses of ovarian and deep infiltrating endometriosis were identified firstly. The diagnosis of peritoneal endometriosis was identified second. Third, those not identified in the previous categories formed the subcohort of other endometriosis. The disease consisting of both ovarian and deep infiltrating endometriosis formed the subcohort of mixed endometriosis.

To assess information on incident cancers, the endometriosis cohort was linked to the Finnish Cancer Registry, which keeps a register of all diagnosed cancers and precancerous stages in Finland from 1953 onward and represents high quality in completeness and accuracy of the registered data.[16,17] The registry includes the personal identity code, the date of cancer diagnosis, and topography and morphology of the specified cancers. The follow-up started on the index day and ended on the day of emigration, death, or December 31, 2014, whichever came first. Information on emigration and death was received from the Finnish Population Register Center. When assessing risk of cancers of the uterine corpus and of the cervix, the follow-up ended in hysterectomy among the endometriosis cohort. Similarly, when assessing risk of ovarian cancer and borderline tumors of the ovary, the follow-up ended in unilateral or bilateral oophorectomy among the endometriosis cohort. Dates of hysterectomies and oophorectomies were detected from the Finnish Hospital Discharge Register using the specific procedural codes.

The data on hysterectomies and oophorectomies from the years before our study were not available, which may underestimate the standardized incidence ratio for uterine, cervical, and ovarian cancer and borderline tumors of the ovary. In addition, hysterectomies and oophorectomies in the Finnish female population were not available, which lowers the population reference rates.[18] Consequently, the standardized incidence ratios for uterine, cervical, and ovarian cancers in this study are slightly too high.

Table 1. The Formation of the Subcohorts of Endometriosis According to the International Classification of Diseases, 9th and 10th Revisions, and the Possible Additional Subsidiary Diagnosis of Endometriosis

Subcohort of Endometriosis	ICD, 9th Revision	ICD, 10th Revision	Possible Additional Subsidiary Diagnosis of Endometriosis
Ovarian	6171A	N80.1	Peritoneal, other
Deep infiltrating			Peritoneal, other
Rectovaginal	6174A	N80.4	
Intestine	6175A	N80.5	
Bladder	—	N80.80	
Sacrouterine ligaments	—	N80.81	
Mixed			Peritoneal, other
(Ovarian concomitantly with deep infiltrating)[1]	6171A+	N80.1+	
	6174A/6175A	N80.4/N80.5/N80.80/N80.81	
Peritoneal			Other
Tubal	6172A	N80.2	
Peritoneal	6173A	N80.3	
Retrouterinal	6173B	—	
Other			—
Cicatrix cutis	6176A	N80.6	
Other specified	6178X	N80.8, N80.89	
Other unspecified	6179X	N80.9	

ICD, International Classification of Diseases.
Dash indicates that there is no similar diagnosis in this revision of the ICD or lack of possible additional subsidiary diagnosis.

Person-years of follow-up were calculated by 5-year age categories and calendar periods and by time since the index day (less than 0.5, 0.5–4.9, 5–9.9, 10 years or greater). The standardized incidence ratio was calculated as the ratio between the observed and the expected number of cancers in each stratum. The expected number was defined by multiplying the accumulated person-years of

Table 2. Number of Women With Surgically Verified Endometriosis by Age at Index Procedure and the Number of Person-Years by Age at Follow-up

	Whole Cohort			Subtype of Endometriosis		
Age (y)	All	Censored at Hysterectomy	Censored at Oophorectomy	Ovarian	Peritoneal	Deep
No. of women						
10–19	525 (1)	522 (1)	502 (1)	121 (1)	343 (2)	24 (1)
20–29	12,685 (25)	12,638 (36)	12,044 (33)	4,888 (21)	5,835 (29)	839 (35)
30–39	18,027 (36)	15,775 (45)	15,501 (42)	7,896 (34)	7,673 (38)	865 (36)
40–49	15,286 (31)	5,778 (16)	7,872 (22)	8,249 (36)	5,374 (27)	514 (22)
50–59	2,985 (6)	560 (2)	539 (1)	1,800 (8)	850 (4)	109 (5)
60 or more	425 (1)	99 (0)	66 (0)	256 (1)	112 (1)	21 (1)
All	49,933 (100)	35,372 (100)	36,524 (100)	23,210 (100)	20,187 (100)	2,372 (100)
Person-years by age						
10–19	676 (0)	666 (0)	639 (0)	154 (0)	446 (0)	34 (0)
20–29	51,212 (6)	50,905 (10)	48,139 (9)	18,268 (5)	25,326 (7)	3,286 (11)
30–39	186,115 (22)	172,793 (36)	165,870 (30)	74,168 (19)	86,189 (24)	10,111 (35)
40–49	263,145 (31)	162,291 (33)	187,324 (34)	117,459 (31)	117,878 (32)	8,362 (29)
50–59	220,562 (26)	76,401 (16)	112,703 (20)	109,863 (29)	91,023 (25)	4,993 (17)
60 or more	116,975 (14)	22,296 (5)	41,695 (7)	62,810 (16)	44,574 (12)	2,150 (7)
All	838,685 (100)	485,351 (100)	556,370 (100)	382,721 (100)	365,436 (100)	28,936 (100)

Data are n (column %).

Table 3. Female Genital Cancers and Precancerous Conditions for the Endometriosis Cohort

Cancer Type or Site	Observed No.	Expected No.	Ratio of Observed to Expected	95% CI
Cervix uteri*	28	37.1	0.76	0.50–1.09
Adenocarcinoma	11	10.4	1.06	0.53–1.88
Squamous cell carcinoma	8	17.2	0.46	0.20–0.91
Other	9	9.43	0.95	0.44–1.81
Corpus uteri*	65	62.4	1.04	0.80–1.32
Endometrioid	54	50.8	1.06	0.80–1.38
Other	11	11.6	0.95	0.47–1.70
Ovary†	129	73.2	1.76	1.47–2.08
Serous	50	36.5	1.37	1.02–1.80
Mucinous	10	11.3	0.88	0.42–1.62
Endometrioid	33	10.6	3.12	2.15–4.38
Clear cell	21	4.06	5.17	3.20–7.89
Other	15	10.8	1.40	0.78–2.30
Other female genital organs‡	37	38.0	0.97	0.69–1.34
Vulva	12	16.1	0.75	0.39–1.30
Vagina	6	4.2	1.43	0.52–3.10
Others	19	17.7	1.07	0.65–1.68
Not included above§				
Cervix uteri, noninvasive neoplasms*§‖	221	271.4	0.81	0.71–0.92
Borderline tumor of the ovary†§	46	35.5	1.29	0.95–1.72

Follow-up ended in death, emigration, or on December 31, 2014. The number of person-years is 838,685 (N=49,933).
* Women who underwent hysterectomy at the primary operation were excluded; follow-up ended in hysterectomy. The number of person-years was 485,351 (n=35,372).
† Women who underwent oophorectomy at the primary operation were excluded; follow-up ended in oophorectomy. The number of person-years was 556,370 (n=36,524).
‡ Neoplasms of vulva, vagina, and female genital organs of unspecified origin.
§ Defined as precancerous conditions.
‖ In situ carcinomas from the mid-1960s, dysplasia gravis lesions since 1988 (defined as cervical intraepithelial neoplasia III 1991).

follow-up in each stratum by the cancer incidence rate in the corresponding Finnish female population. The 95% CIs for the standardized incidence ratio were based on the assumption that the number of observed cases followed a Poisson distribution. The correction for multiple testing was not used here because of the explorative character of the study.

RESULTS

Table 2 summarizes the age distribution of the women with endometriosis at the index day and in person-years by age at follow-up. The median age at baseline was 36.4 years in the analyses without excluding women with hysterectomy or oophorectomy before the index day. Twenty-six percent of the women were younger than 30 years of age and less than 1% older than 60 years on the index day. There were 838,685 person-years of follow-up with a mean follow-up of 16.8 years. The number of person-years decreased to 485,351 when the follow-up ended with hysterectomy and to 556,370 when the follow-up ended at oophorectomy (Table 2).

The number of observed and expected cases of various gynecologic cancers for the entire cohort is shown in Table 3 and for subtypes of endometriosis in Table 4. Altogether, 259 cases of gynecologic cancer were observed, whereas the expected number was 210.7.

Endometriosis was associated with a significantly increased risk of ovarian cancer in the whole cohort (standardized incidence ratio 1.76 [95% CI 1.47–2.08]). Specifically, the risk of ovarian cancer with serous (1.37 [1.02–1.80]), endometrioid (3.12 [2.15–4.38]), and clear cell (5.17 [3.20–7.89]) histology was increased (Table 3). The standardized incidence ratio of ovarian cancer was increased in the subtype of ovarian endometriosis, especially for endometrioid (4.72 [2.75–7.56]) and clear cell (10.1 [5.50–16.9]) histology. Peritoneal endometriosis was associated with an increase in risk for the endometrioid histologic type of ovarian cancer (2.03 [1.05–3.54]) (Table 4). There was no association between deep infiltrating endometriosis and the risk of ovarian cancer.

After 5–10 years of follow-up, the risk of ovarian cancer significantly increased (Table 5). The increased standardized incidence ratio resulted mainly from the excess of endometrioid and clear cell ovarian cancer

Table 4. Female Genital Cancers and Precancerous Stages, the Observed Number of Cancer Cases, and Their Standardized Incidence Ratios and 95% CIs According to Type of Endometriosis and Histology

	Type of Endometriosis								
	Ovarian (n=23,210)			Peritoneal (n=20,187)			Deep (n=2,372)		
Cancer Type or Site	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Cervix uteri*	15	0.96	0.54–1.58	9	0.53	0.24–1.00	3	1.80	0.37–5.25
Adenocarcinoma	4	0.91	0.25–2.32	5	1.05	0.34–2.45	1	2.17	0.05–12.1
Invasive squamous cell carcinoma	4	0.55	0.15–1.41	2	0.25	0.03–0.90	2	2.75	0.33–9.93
Other	7	1.80	0.72–3.70	2	0.47	0.06–1.68	0	0.00	0.00–7.69
Corpus uteri*	33	1.12	0.77–1.57	29	1.04	0.70–1.49	1	0.74	0.02–4.12
Endometrioid	27	1.12	0.74–1.62	24	1.06	0.68–1.58	1	0.95	0.02–5.26
Other	6	1.13	0.41–2.46	5	0.96	0.31–2.24	0	0.00	0.00–12.7
Ovary†	64	2.56	1.98–3.27	54	1.32	0.99–1.72	3	1.41	0.29–4.10
Serous	20	1.62	0.99–2.49	25	1.21	0.79–1.79	2	2.05	0.25–7.41
Mucinous	5	1.29	0.42–3.01	5	0.80	0.26–1.86	0	0.00	0.00–9.58
Endometrioid	17	4.72	2.75–7.56	12	2.03	1.05–3.54	1	3.35	0.08–18.7
Clear cell	14	10.1	5.50–16.9	6	2.67	0.98–5.81	0	0.00	0.00–28.2
Other	8	2.16	0.93–4.26	6	1.02	0.37–2.21	0	0.00	0.07–10.5
Other female genital organs‡	21	1.09	0.68–1.67	12	0.78	0.40–1.36	2	0.89	0.27–8.14
Vulva	7	0.87	0.35–1.78	4	0.61	0.17–1.57	1	2.62	0.07–14.6
Vagina	4	1.92	0.52–4.90	1	0.58	0.01–3.24	0	0.00	0.00–33.6
Other	10	1.11	0.53–2.03	7	0.99	0.40–2.04	1	2.50	0.06–13.9
Not included above§									
Cervix uteri, noninvasive neoplasms*§‖	82	0.75	0.60–0.92	109	0.88	0.72–1.05	12	0.78	0.40–1.36
Borderline tumor of ovary†§	20	1.63	1.00–2.52	24	1.25	0.80–1.85	0	0.00	0.00–2.65

SIR, standardized incidence ratio.
Follow-up ended in death, emigration, or on December 31, 2014.
* Women who underwent hysterectomy at the primary operation were excluded. Follow-up ended in hysterectomy. Ovarian endometriosis (n=15,270), 202,701 person-years; peritoneal (n=15,331), 227,676 person-years; deep (n=1,810), 19,405 person-years.
† Women who underwent oophorectomy at the primary operation were excluded. Follow-up ended in oophorectomy. Ovarian endometriosis (n=13,505), 192,257 person-years; peritoneal endometriosis (n=17,747), 298,374 person-years; and deep (n=2,058), 23,213 person-years of follow-up.
‡ Neoplasms of vulva, vagina, and female genital organs of unspecified origin.
§ Defined as precancerous conditions.
‖ In situ carcinomas from the mid-1960s, dysplasia gravis lesions since 1988 (defined as cervical intraepithelial neoplasia III 1991).

risk in ovarian and peritoneal types of endometriosis. An increased standardized incidence ratio during the first 6 months of follow-up was explained by four excess cases of ovarian cancer, three within the subtype of ovarian and one within peritoneal endometriosis.

In women with ovarian endometriosis, we found no major variation in the standardized incidence ratios for endometrioid and clear cell histology of ovarian cancer according to the age at cancer diagnosis (Table 6). The increased risk of borderline tumors of the ovary concerned the cohort of ovarian endometriosis (1.63 [1.00–2.52]) (Tables 3 and 4). The standardized incidence ratio was increased only during the first half year after the diagnosis.

Endometriosis was not associated with an altered standardized incidence ratio of cervical cancer in the entire cohort nor in any of the different subtypes of endometriosis. However, a decreased standardized incidence ratio for squamous cell cervical cancer was observed in the whole cohort (0.46 [0.20–0.91]), and especially in cases of peritoneal endometriosis (0.25 [0.03–0.90]). A decreased risk was also seen for the noninvasive neoplasms of the cervix (0.81 [0.71–0.92]) among the whole cohort and in women with ovarian endometriosis (0.75 [0.60–0.92]) (Tables 3 and 4).

None of the subtypes of endometriosis differed from the female population regarding risks for endometrial cancers or other uterine cancers (Table 4) nor

Table 5. Time From Endometriosis Diagnosis According to the Histology and Type of Endometriosis: the Number of Observed Ovarian Cancer Cases, the Standardized Incidence Ratios, and Their 95% CIs

Histology and Time From Endometriosis Diagnosis (y)	Type of Endometriosis											
	All (n=36,524)			Ovarian (n=13,505)			Peritoneal (n=17,747)			Deep (n=2,058)		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
All												
Less than 0.5	5	4.58	1.49–10.7	3	7.40	1.53–21.6	1	1.85	0.05–10.3	0	0.00	0.00–68.8
0.5–4.9	18	1.56	0.93–2.46	8	1.90	0.82–3.74	8	1.36	0.59–2.68	0	0.00	0.00–7.03
5–9.9	20	1.30	0.79–2.00	12	2.21	1.14–3.85	8	0.98	0.42–1.93	0	0.00	0.00–5.94
10 or greater	86	1.90	1.52–2.35	41	2.75	1.97–3.73	37	1.40	0.99–1.93	3	3.21	0.66–9.36
Serous												
Less than 0.5	1	2.19	0.06–12.2	0	0.00	0.00–21.9	1	4.37	0.11–24.4	0	0.00	0.00–172
0.5–4.9	7	1.40	0.56–2.89	3	1.66	0.34–4.84	3	1.17	0.24–3.41	0	0.00	0.00–17.1
5–9.9	7	0.99	0.40–2.03	4	1.61	0.44–4.11	3	0.79	0.16–2.31	0	0.00	0.00–13.8
10 or greater	35	1.46	1.02–2.03	13	1.64	0.87–2.80	18	1.29	0.76–2.03	2	4.25	0.51–15.4
Endometrioid												
Less than 0.5	1	6.10	0.15–34.0	0	0.00	0.00–61.0	0	0.00	0.00–43.8	0	0.00	0.00–568
0.5–4.9	6	3.44	1.26–7.49	2	3.16	0.38–11.4	4	4.42	1.21–11.3	0	0.00	0.00–54.3
5–9.9	6	2.48	0.91–5.40	3	3.50	0.72–10.2	3	2.34	0.48–6.84	0	0.00	0.00–39.4
10 or greater	20	3.21	1.96–4.95	12	5.86	3.03–10.2	5	1.37	0.44–3.19	1	7.69	0.19–42.9
Clear cell												
Less than 0.5	1	29.30	0.74–163	1	73.9	1.87–411	0	0.00	0.00–241	0	0.00	0.00–1690
0.5–4.9	1	2.10	0.05–11.7	1	5.52	0.14–30.7	0	0.00	0.00–16.2	0	0.00	0.00–144
5–9.9	4	4.85	1.32–12.4	4	13.4	3.65–34.3	0	0.00	0.00–8.80	0	0.00	0.00–93.0
10 or greater	15	5.50	3.08–9.06	8	8.89	3.84–17.5	6	3.79	1.39–8.24	0	0.00	0.00–58.0

SIR, standardized incidence ratio.

Women who underwent oophorectomy in the primary operation were excluded; follow-up ended in oophorectomy, death, emigration, or on December 31, 2014. All endometriosis person-years, 556,370; ovarian, 192,257 person-years; peritoneal, 298,374 person-years; deep, 23,213 person-years.

was endometriosis associated with risk of cancer in other female genital organs (such as the vulva or vagina).

DISCUSSION

Ovarian endometriosis was associated with an increased risk of ovarian cancer, especially that of endometrioid and clear cell histology. No increase in overall risk of ovarian cancer was evident among women with peritoneal and deep infiltrating endometriosis. The risk of endometrial cancer was unaltered, and the risk for precancerous cervical lesions and for squamous cell carcinoma of the cervix was reduced.

The strengths of this study are the nationwide cohort and the population-based registers known for their completeness and high quality.[15,16] Unlike many studies, we only included women with surgically verified disease, which may represent more severe endometriosis.[19–21] Nonetheless, 37% of our cohort had endometriosis as a subsidiary diagnosis and 21% underwent day surgeries from 1994 onward, which may represent less symptomatic forms of the disease. A weakness of this study is the almost three decades of time during which the diagnostics, treatment indications as well as medical and surgical treatments of endometriosis have evolved greatly, which may affect the results. Moreover, testing for multiple associations may have produced some false-positive results.

The key finding was that especially ovarian endometriosis carries an increased standardized incidence ratio (2.6-fold) for ovarian cancer. Similar associations between ovarian endometriosis and ovarian cancer (two- and threefold) have been seen in two population-based studies.[19,20] In our study, standardized incidence ratios of endometrioid and clear cell ovarian cancer were high (three- and fivefold), and when focusing on ovarian endometriosis, standardized incidence ratios were five- and 10-fold, which is higher than previously reported.[5,7,21] The increase in risk started from 5 years after endometriosis surgery and from the age of 30 years onward. Previously the highest risk has been associated with long-lasting and early-onset endometriosis disease.[20]

Borderline ovarian tumors were also significantly elevated in our study during the first 6 months of follow-up in the subgroup of ovarian endometriosis. This is an interesting finding because the pathogenesis of endometriosis-associated cancers has been proposed to develop through borderline tumors.[22] We also observed a slight increase in risk for serous

Table 6. Age at Ovarian Cancer Diagnosis According to the Histology and Type of Endometriosis: the Observed Number of Cancer Cases, Their Standardized Incidence Ratios, and 95% CIs

Histology and Age at Ovarian Cancer (y)	Type of Endometriosis											
	All (n=36,524)			Ovarian (n=13,505)			Peritoneal (n=17,747)			Deep (n=2,058)		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95%CI	Observed	SIR	95% CI
All												
20–29	0	0.00	0.00–3.18	0	0.00	0.00–9.52	0	0.00	0.00–6.19	0	0.00	0.00–47.7
30–39	13	1.69	0.90–2.88	9	3.26	1.49–6.19	4	1.02	0.28–2.61	0	0.00	0.00–9.17
40–49	46	2.05	1.50–2.73	24	3.17	2.03–4.70	16	1.28	0.73–2.08	0	0.00	0.00–5.06
50–59	47	1.76	1.29–2.34	21	2.37	1.47–3.62	24	1.56	1.00–2.31	1	1.55	0.04–8.65
60 or older	23	1.51	0.96–2.27	10	1.87	0.89–3.43	10	1.17	0.56–2.16	2	7.14	0.87–25.8
Serous												
20–29	0	0.00	0.00–11.8	0	0.00	0.00–35.3	0	0.00	0.00–22.7	0	0.00	0.00–187
30–39	4	1.33	0.36–3.40	2	1.88	0.23–6.77	2	1.28	0.15–4.61	0	0.00	0.00–25.9
40–49	14	1.39	0.76–2.33	6	1.77	0.65–3.86	5	0.88	0.29–2.06	0	0.00	0.00–12.1
50–59	19	1.36	0.82–2.13	7	1.52	0.61–3.12	11	1.37	0.68–2.44	1	2.97	0.08–16.6
60 or older	13	1.42	0.76–2.43	5	1.56	0.51–3.64	7	1.36	0.55–2.80	1	5.88	0.15–32.8
Endometrioid												
20–29	0	0.00	0.00–74.6	0	0.00	0.00–215	0	0.00	0.00–151	0	0.00	0.00–1060
30–39	4	6.02	1.64–15.4	3	12.5	2.57–36.5	1	2.99	0.08–16.7	0	0.00	0.00–104
40–49	13	3.24	1.72–5.53	6	4.41	1.62–9.59	5	2.24	0.73–5.23	0	0.00	0.00–28.2
50–59	12	2.79	1.44–4.86	6	4.19	1.54–9.10	6	2.42	0.89–5.25	0	0.00	0.00–36.8
60 or older	4	2.61	0.71–6.69	2	3.70	0.45–13.4	0	0.00	0.00–4.39	1	33.3	0.84–186
Clear cell												
20–29	0	0.00	0.00–98.4	0	0.00	0.00–266	0	0.00	0.00–229	0	0.00	0.00–995
30–39	2	9.20	1.11–33.2	2	24.5	2.96–88.3	0	0.00	0.00–36.7	0	0.00	0.00–242
40–49	8	5.15	2.22–10.2	6	11.2	4.12–24.4	2	2.39	0.29–8.62	0	0.00	0.00–60.2
50–59	10	6.50	3.12–11.9	6	11.8	4.32–25.6	3	3.38	0.70–9.87	0	0.00	0.00–98.8
60 or older	1	1.39	0.04–7.74	0	0.00	0.00–14.8	1	2.50	0.06–13.9	0	0.00	0.00–369

SIR, standardized incidence ratio.

Women who underwent oophorectomy at the primary operation were excluded; follow-up ended in oophorectomy, death, emigration, or on December 31, 2014. All endometriosis cases contributed to 556,370 person-years of follow-up: ovarian endometriosis 192,257 person-years; peritoneal 298,374 person-years; and deep 23,213 person-years of follow-up.

ovarian carcinomas (standardized incidence ratio 1.4), which is in line with a pooled analysis of case–control studies from the United States showing an association with low-grade serous carcinomas (standardized incidence ratio 2.1).[7]

Our study evaluated cancer risk separately for patients with peritoneal and deep infiltrating endometriosis. Previously, a small increase in risk of ovarian cancer with nonovarian endometriosis (1.5-fold) has been shown in a Swedish study.[20] In our study, the risk of ovarian cancer in nonovarian types of endometriosis did not differ from the overall female population. However, the peritoneal type showed a slightly increased risk of ovarian cancer with endometrioid histology (standardized incidence ratio 2.1) and with clear cell histology after 10 years of follow-up (standardized incidence ratio 3.8). Because of the infiltrative behavior of deep infiltrating endometriosis, there is a special interest to assess its associations with cancer. However, because the deep infiltrating diagnosis has been reliably used only after the mid-1990s, the cohort remained quite small (n=2,372) and the mean follow-up was only 12.2 years. Based on these results, we conclude that the risks of gynecologic cancers associated with deep infiltrating endometriosis are not increased in the short term, but a larger cohort with longer follow-up is needed to reliably assess the risks associated with long-standing disease.

We found a strongly decreased risk of cervical cancer of squamous cell histology among women with endometriosis, especially with peritoneal endometriosis. A larger number of Pap tests may not be the explanation for this phenomenon because the risk of precancerous lesions of the cervix was also decreased. Similarly, a decreased risk of cervical cancer and the precancerous lesions has been reported previously in Sweden.[20] Because the main cause is human papillomavirus, one explanation might be reduced sexual activity, for example, as a result of pelvic pain, and thus lower exposure to the viruses.[23,24] However, more complex immunologic mechanisms may also be involved with diseases of chronic inflammation.

The risk of endometrial cancer did not differ from the population. One previous study[25] has reported a reduced risk of endometrial cancer (odds ratio 0.58). Other studies have found no

association,[19,20,26,27] or even an excess risk of endometrial cancer.[21,28,29]

It is important to note that even if some ovarian cancer standardized incidence ratios are high, the absolute excess risk of ovarian cancer in the whole cohort is quite small, approximately one excess case among 1,000 patients with endometriosis during 10 years of follow-up and for patients with ovarian endometriosis, approximately two cases per 1,000 patients.

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